

A follow-up on desiderosmia (olfactory craving), a novel symptom associated with iron deficiency anemia

To the Editor:

As a sequel to our previous study,¹ we would like to further comment on the topic of desiderosmia (olfactory cravings). We previously described three patients with iron deficiency anemia (IDA) presenting with symptoms of olfactory cravings, with compulsion to smell a variety of substances. We have designated the name, “desiderosmia,” for this novel symptom. After treatment for IDA, the patients’ olfactory craving symptoms resolved.

In this article, we reviewed English medical literature and the World Wide Web to determine if such olfactory cravings associated with iron deficiency anemia had been previously reported. We searched the PubMed, Google, and Google Scholar to find publications, reports, presentations, or testimonies of individuals in online blogs using a combination of search terms including “nasal,” “olfactory,” “smell,” “craving,” “iron deficiency,” and “anemia.”

Although this specific symptom has only been previously published once in medical literature,¹ we did find a large number of online patients self-reporting such a phenomenon potentially corroborating our practice experience. Upon further exploration using Google search engine, we came across a number of online blog posts, mostly in pregnancy blogs, in which participants described this unique symptom.^{2,3} These women reported powerful cravings of olfaction, and were frequently overtaken by a strong desire to smell certain odors. The types of substances craved and their associated medical conditions (when reported) are summarized in Supporting Information Table S1.




The effects of IDA on the olfactory system have only been minimally explored. It is known that several key enzymes necessary for proper olfaction such as neuronal nitric oxide synthase, tryptophan dioxygenase, and tyrosine hydrolase require either heme or inorganic iron for structure or activity.^{4,5} In an animal study, iron-deficient rats were observed to have prolonged exploratory time (sniffing) for attractive odorants compared to controls. The hypothesis was that IDA decreased the activity of these enzymes resulting in a net reduction of inhibitory olfactory inputs.⁶ Another study compared the olfactory function of IDA patients with healthy subjects and found a heightened sensitivity (lower threshold) in detecting odorant among patients with IDA. These reports support a plausible association between the physiological changes in olfaction and iron store.

The mystery behind the pathophysiology of this symptom is a driving factor for further research and exploration. Additionally, it would be interesting to investigate what factors potentially account for the

discrepancy between the volume of reports seen in online blogs and those documented in clinical practice. Perhaps these symptoms are being overlooked or not screened for in clinical encounters, and therefore leading to a misunderstanding of this symptom in practice. By placing a name to this symptom, we hope to contribute to a better understanding and recognition of these olfactory cravings by both patients and physicians.

CONFLICTS OF INTEREST

All authors declare no conflicts of interests.

Bryar R. Hansen¹ , Wayne A. Bottner², Aishwarya Ravindran¹ ,
Ramona DeJesus³, Ronald S. Go¹ 

¹Division of Hematology, Mayo Clinic, Rochester, Minnesota

²Division of Hematology, Gundersen Health System, La Crosse, Wisconsin

³Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota

Correspondence

Ronald S. Go, Division of Hematology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

Email: go.ronald@mayo.edu

REFERENCES

- [1] Hansen BR, Bottner WA, Ravindran A, et al. Desiderosmia (olfactory craving): A novel symptom associated with iron deficiency anemia. *Am J Hematol*. 2017;92:E93–E94.
- [2] <http://www.medhelp.org/posts/Nutrition/Are-weird-cravings-sign-of-possible-mineral-deficiency/show/2279>. Accessed on 1 March, 2017.
- [3] http://www.babycenter.com/400_im-having-weird-smell-cravings-normal-or-not_6731350_785.bc. Accessed on 5 March, 2017.
- [4] Guillemain GJ, Cullen KM, Lim CK, et al. Characterization of the kynurenine pathway in human neurons. *J Neurosci*. 2007;27:12884–12892.
- [5] Matsuo R, Ito E. A novel nitric oxide synthase expressed specifically in the olfactory center. *Biochem Biophys Res Commun*. 2009;386:724–728.
- [6] Ruvin Kumara VM, Wessling-Resnick M. Influence of iron deficiency on olfactory behavior in weanling rats. *J Behav Brain Sci*. 2012;2:167–175.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Autoimmune neutropenia of childhood secondary to other autoimmune disorders: Data from the Italian neutropenia registry

TABLE 1 Characteristics of study populations

	Primary (263)	Secondary (26)	p
Sex (F%)	41.4%	61.5%	0.049
Onset (years, median)	0.77	10.07	1.12e-12
Diagnosis (years, median)	1.09	10.98	2.03e-13
BM aspiration	35.1%	65.4%	0.0024
G-CSF	6.9%	23.1%	0.0045
Severe infections	11.8%	40.0%	0.0001
Recovery	74.9%	7.7%	2.26e-12
SIgAD	3.0%	13.6%	0.015
DAT+	4.1%	50%	1.37e-08
ANC (median) at onset	$0.45 \times 10^9/L$	$0.63 \times 10^9/L$	0.035
WBC (median) at onset	$5.93 \times 10^9/L$	$2.48 \times 10^9/L$	2.81e-11
Leucopenia at onset	39.0%	92.3%	1.80e-07
AMC (median) at onset	$0.62 \times 10^9/L$	$0.34 \times 10^9/L$	9.89e-07
Monocytosis at onset	20.6%	3.8%	0.039
ALC (median) at onset	$4.36 \times 10^9/L$	$1.58 \times 10^9/L$	6.29e-11
High IgG at onset	6.5%	4.5%	0.71

ALC, Absolute Lymphocyte Count; ANC, Absolute Neutrophil Count; AMC, Absolute Monocyte Count; BM, Bone Marrow; DAT, Direct Anti-globulin Test; G-CSF, Granulocyte-Colony Stimulating Factor; IgG, Immunoglobulin G; SIgAD, Selected IgA Deficiency; WBC, White Blood Cells Count.

To the Editor:

Neutropenia is defined by a reduction of Absolute Neutrophil Count (ANC). Among Caucasian people the lower normal limit of ANC in children up to the age of 1 year is $1.0 \times 10^9/L$, whereas from >1 year to adulthood it is $1.5 \times 10^9/L$; neutropenia is defined as mild in case of ANC between 1.0 and $1.5 \times 10^9/L$, moderate with ANC between 0.5 and $1.0 \times 10^9/L$, and severe with ANC $<0.5 \times 10^9/L$.¹ Autoimmune Neutropenia (AIN) is due to auto-antibodies against Human Neutrophil Antigens: the most frequent AIN in childhood is the primary type (p-AIN),²⁻⁴ whereas in adulthood AIN is mostly represented⁵ by secondary neutropenia which can be associated with infection, drug administration, immunodeficiency, neoplasm, bone marrow transplantation (BMT) and autoimmune disorders.^{3,5,6} No specific study about AIN secondary to autoimmune diseases (s-AIN) in childhood has been published yet. In the present paper we describe the natural history of 26 patients affected by s-AIN, whose clinical characteristics were compared with those of a group of 263 children affected by p-AIN: all cases of AIN associated with infection, neoplasm, BMT, drug administration and immunodeficiency other than selected IgA deficiency (SIgAD) were excluded.

Some results are shown in Table 1, whereas more specific characteristics of s-AIN patients are presented in Supporting Information Table S1; the median follow-up in p-AIN and s-AIN cohort was 1.30 years and 4.10 years respectively. A significantly higher prevalence of the female sex in s-AIN was observed ($P = .049$). At appearance in p-AIN cohort the median ANC was $0.45 \times 10^9/L$ (range $0-1.49 \times 10^9/L$), and the neutropenia was severe in 56.3%, moderate in 36.1% and mild in 7.6%, whereas in s-AIN cohort the median ANC was $0.63 \times 10^9/L$ (range

$0.3-1.40 \times 10^9/L$) and the neutropenia was severe in 42.3%, moderate in 46.2% and mild in 11.5%: the difference of ANC at onset between p-AIN and s-AIN was significant ($P = .035$) but there was no significant difference in terms of type of neutropenias (from severe to mild) ($P = .3787$). Median white blood cells count and median absolute lymphocyte count (ALC) at onset were $5.93 \times 10^9/L$ vs. $2.48 \times 10^9/L$ ($P = 2.81e-11$) and $4.36 \times 10^9/L$ vs. $1.58 \times 10^9/L$ ($P = 6.29e-11$) in p-AIN and s-AIN patients respectively. In s-AIN all lymphocytes sub-classes (CD3, CD19, CD4, CD8, CD56) were reduced as compared to p-AIN, with CD19 more decreased than CD3 lymphocytes: the median CD19 count was $0.242 \times 10^9/L$ in s-AIN group vs. $0.934 \times 10^9/L$ in p-AIN group ($P = 8.13e-10$) whereas the median CD3 count was $1.385 \times 10^9/L$ in s-AIN group vs. $2.824 \times 10^9/L$ in p-AIN group ($P = 2.32e-06$). Leucopenia for age was more frequent in s-AIN vs. p-AIN (92.3% vs. 39.0%; $P = 1.80e-07$) whereas monocytosis for age occurred more often in p-AIN vs. s-AIN (20.6% vs. 3.8%; $P = .039$).

The frequency of children who were born preterm and then developed p-AIN or s-AIN was 12.85% and 3.84% respectively: the prevalence of former preterm babies among p-AIN patients was significantly higher than in a cohort of 487 children consecutively hospitalized for various reasons in a pediatric center: 12.85% vs. 6.98% ($P = .008362$). There was no significant difference comparing s-AIN and the same group of control children ($P = .5367$).

The prevalence of SIgAD (confirmed in at least two dosages) was 3% in p-AIN and 13.6% in s-AIN children and both prevalences were significantly higher than that observed (0.21%) in a group of 470 laboratory controls ($P = .0009$ in p-AIN and $P = 7.239e-12$ in s-AIN): the co-existence with SIgAD was significantly higher in s-AIN than in p-AIN ($P = .015$). Increased level of IgG was found in 6.5% of p-AIN

and 4.5% of s-AIN respectively ($P = .71$). Bone Marrow examination was done in 35.1% of p-AIN patients and in 65.4% of s-AIN patients ($P = .0024$) and in all but three p-AIN patients it showed normal or increased cellularity: in these three children a moderate decrease of myeloid cellularity was observed.

An infection was arbitrarily defined as "severe" in the presence of a final diagnosis of sepsis, pneumonia, skin/soft tissue abscesses, osteomyelitis, otomastoiditis or meningitis/encephalitis: 11.8% of the p-AIN and 40.0% of the s-AIN children suffered from severe infections ($P = .0001$). Lymphocytopenia and the rarity of monocytosis might contribute to the significantly higher infection load of s-AIN over p-AIN.

At the time of the analysis 74.9% of p-AIN and 7.7% of s-AIN patients had recovered from neutropenia ($P = 2.26e-12$). Only 2 children recovered from s-AIN: one was a patient with autoimmune thyroiditis (AT) and celiac disease (CD) who, after starting gluten-free diet recovered from AIN and the second one was a boy who recovered from Evans Syndrome (ES). The Kaplan Meier recovery curve is shown in Supporting Information Figure S1. Among p-AIN children with at least 5 years of Follow-Up 94.1% had recovered from neutropenia.

Neutropenia appeared contemporarily to other autoimmune manifestations in 11/26 s-AIN patients (42.3%), appeared firstly in 8/26 patients (30.7%) (median and mean time of appearance of other autoimmune signs: 440 and 987 days respectively) and later in 7/26 patients (26.9%) (median and mean time of appearance of s-AIN: 558.5 and 865.3 days respectively). In 8 s-AIN patients neutropenia remained isolated, sometimes for 6–7 years, before the appearance of other autoimmune manifestations. ES (11 patients) and AT (7 patients) were the most common presentation of s-AIN. Some s-AIN children showed a not previously reported association with growth hormone deficiency (3), CD (2) and autoimmune encephalitis (1). Furthermore, in the s-AIN cohort 14 patients showed positivity of antinuclear antibodies (ANA) higher than 1:80, 6 patients presented an association with more than one defined autoimmune disorder and in 4 girls neutropenia was in a context of not defined autoimmune disease characterized by arthralgia and ANA positivity.

Among s-AIN patients intravenous immunoglobulin and intravenous or oral steroids were used in 10 patients with the goal of treating autoimmune disorders other than AIN. Among children affected by ES 2 were treated also with mycophenolate mofetil, one with rituximab and another one with splenectomy. Furthermore, the girl presenting an autoimmune hepatitis was treated with cyclosporine and mycophenolate mofetil. Antibiotic prophylaxis was never administered and Granulocyte Colony Stimulating Factor was used in 6.9% of p-AIN and 23.1% of s-AIN patients respectively ($P = .0045$): in all of them a rise in ANC was obtained.

In conclusion, p-AIN is in the vast majority of cases a benign and self-limiting disorder typically occurring under 2–3 years of age whereas s-AIN is a more severe disease, usually presenting after first 5 years of life and with a highly frequent tendency to become chronic.


ACKNOWLEDGMENTS

ERG spa, Rimorchiatori Riuniti, Cambiaso & Risso, SAAR Depositi Oleari Portuali, are acknowledged for supporting the work of the Hematology Unit of G. Gaslini Institute. No specific funding was received for this study. The Sicilian Primary Immunodeficiency Association is acknowledged for

supporting the work of the Pediatric Oncology-Hematology Unit of A.R.N. A.S. Civico Hospital. No specific funding was received for this study. Preliminary results of this study have been submitted as an abstract at 22th EHA Congress (Madrid, Spain, 22–25 June 2017).

CONFLICT OF INTERESTS

The authors report no potential conflicts of interest, including specific financial interest, relationships, or affiliations relevant to the subject of this manuscript.

Piero Farruggia¹ , Giuseppe Puccio², Francesca Fioredda³, Tiziana Lanza³, Laura Porretti⁴, Ugo Ramenghi⁵, Angelica Barone⁶, Sonia Bonanomi⁷, Andrea Finocchi⁸, Roberta Ghilardi⁹, Saverio Ladogana¹⁰, Nicoletta Marra¹¹, Baldassare Martire¹², Lucia Dora Notarangelo¹³, Daniela Onofriello¹⁴, Marta Pillon¹⁵, Giovanna Russo¹⁶, Laura Lo Valvo¹⁶, Jessica Serafinelli⁸, Fabio Tucci¹⁷, Fiammetta Zunica¹³, Federico Verzegnassi¹⁸, Carlo Dufour³

¹Pediatric Hematology and Oncology Unit, A.R.N.A.S. Ospedale Civico, Palermo, Italy

²Department of Sciences for Health Promotion, University of Palermo, Italy

³Clinical and Experimental Hematology Unit, G. Gaslini Children's Hospital, Genova, Italy

⁴Flow Cytometry Service, Laboratory of Clinical Chemistry and Microbiology, IRCCS "Ca' Granda" Foundation, Maggiore Hospital Policlinico, Milan, Italy

⁵Ematologia, Dipartimento di Scienze Pediatriche, Ospedale Infantile Regina Margherita, Torino, Italy

⁶Department of Pediatric Onco-hematology, University Hospital, Parma, Italy

⁷Fondazione MBBM, Clinica Pediatrica, Università di Milano - Bicocca, A. O. San Gerardo, Monza, Italy

⁸Immunologia Pediatrica, Università Tor Vergata, Roma, Italy

⁹Department of Pediatrics, IRCCS "Ca' Granda" Foundation, Maggiore Hospital Policlinico, Milan, Italy

¹⁰Department of Hematology, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy

¹¹A.O.R.N. Santobono Pausillipon, Naples, Italy

¹²Dipartimento di Scienze e Chirurgia Pediatriche, U. O. Oncoematologia Pediatrica, Ospedale Policlinico- Giovanni XXIII, Bari, Italy

¹³Pediatric Oncology-Hematology and BMT Unit, Children's Hospital, Spedali Civili, Brescia, Italy

¹⁴Hematology Unit, Hospital of Pescara, Italy

¹⁵Dipartimento di Oncoematologia Pediatrica, Università di Padova, Italy

¹⁶Pediatric Hematology and Oncology Unit, Policlinico Hospital, University of Catania, Italy

¹⁷Department of Pediatric Onco-Hematology, Meyer Children's Hospital, Florence, Italy

¹⁸Institute of Maternal and Child Health IRCCS Burlo Garofolo, Trieste, Italy

Correspondence

Piero Farruggia, U.O.C. di Oncoematologia Pediatrica, A.R.N.A.S. Ospedali Civico, Di Cristina e Benfratelli, Piazza Nicola Leotta 4, 90127 Palermo, Italy. Email: piero.farruggia@arnascivico.it; pfarruggia@libero.it

REFERENCES

- [1] Dinuer MC. The phagocyte system and disorders of granulopoiesis and granulocyte function. In: Nathan DG, Orkin SH, eds. *Nathan and Oshi's Hematology of Infancy and Childhood*. Philadelphia: WBS saunders Company; 2003: 923–1010.
- [2] Bux J, Behrens G, Jaeger G, Welte K. Diagnosis and clinical course of autoimmune neutropenia in infancy: analysis of 240 cases. *Blood*. 1998;91:181–186.
- [3] Bruin MC, von Dem Borne AE, Tamminga RY, Kleijer M, Buddelmeijer L, de Haas M. Neutrophil antibody specificity in different types of childhood autoimmune neutropenia. *Blood*. 1999;91:1797–1802.
- [4] Farruggia P, Fioredda F, Puccio G, et al. Porretti L, et al. Anza T, Ramenghi U, Ferro F, Macaluso A, Barone A, Bonanomi S, Caruso S, Casazza G, Davitto M, Ghilardi R, Ladogana S, Mandaglio R, Marra N, Martire B, Mastrodicasa E, Dora Notarangelo L, Onofrillo D, Robustelli G, Russo G, Trizzino A, Tucci F, Pillon M, Dufour C. Autoimmune neutropenia of infancy: Data from the Italian neutropenia registry. *Am J Hematol*. 2015;90:E221–E222.
- [5] Capsoni F, Sarzi-Puttini P, Zanella A. Primary and secondary autoimmune neutropenia. *Arthritis Res Ther*. 2005;7:208–214.
- [6] Farruggia P. Immune neutropenias of infancy and childhood. *World J Pediatr*. 2016;12:142–148.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Received: 18 May 2017 | Accepted: 26 May 2017

DOI 10.1002/ajh.24804

Allogeneic hematopoietic cell transplantation in morphologic leukemia-free aplastic state

To the Editor:

The presence of residual disease before allogeneic hematopoietic cell transplantation (allo-HCT) in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) is best assessed in a cellular bone marrow. As a result, HCT is usually postponed until hematopoietic recovery and resolution of aplasia. The available evidence for safety and efficacy of HCT in morphologic leukemia-free aplastic state is limited to sporadic case reports.^{1–3} The generalizability of the available results is limited by potential publication bias because of successful cases having a higher chance of being reported and published. We adopted an unbiased approach and retrospectively reviewed the transplant databases of two large transplant centers.

We limited our search to the period between January 2003 and December 2016, and the transplant databases of both centers (University of Minnesota [Minneapolis, MN], Washington University [St. Louis, MO]) were reviewed. The inclusion criteria were: (i) Age at the time of HCT \geq 18 years, (ii) Diagnosis of AML or MDS, (iii) Bone marrow biopsy

within 30 days prior to allo-HCT demonstrating aplasia in a morphologic leukemia-free state. Aplasia was defined as bone marrow cellularity $<$ 5% and red cell and platelet transfusion dependence. We did not consider a minimum required aplasia duration or last treatment-to-HCT interval. Patients with hematopoietic recovery after the last treatment but aplastic (for any reason) on pre-HCT assessment were not included. The cumulative incidence method was used to estimate relapse while treating non-relapse mortality (NRM) as a competing risk, and to estimate NRM while treating relapse as a competing risk. Kaplan-Meier curves were used to estimate overall survival (OS) and relapse-free survival (RFS). R 3.0.2 was used for analysis.

A total of 18 patients were included, representing 0.8% of all 1,666 patients in the two centers who underwent allo-HCT for AML or MDS within the same time period. Table 1 shows patient and transplant characteristics as well as outcomes. The median (range) age of patients was 57 (24–73) years and 56% were males. Secondary AML was the most common diagnosis ($n = 9$, 50%, including 6 patients transformed from MDS, 1 from aplastic anemia, 1 from myelofibrosis, and 1 from chronic myelomonocytic leukemia), followed by *de novo* AML ($n = 6$, 33%). The remaining patients had *de novo* MDS ($n = 3$, 17%). Adverse-risk cytogenetic/molecular abnormalities were present in 8 (44%) patients. The median (range) number of cycles of treatment (including prior transplantation in four cases) before the development of aplasia was 4 (1–24). The treatment immediately preceding aplasia was intensive chemotherapy in 9 (50%; high-dose cytarabine: 2, 7 + 3: 3, 5 + 2: 1, Cladribine + Cytarabine + Filgrastim + Mitoxantrone [CLAG-M]: 1, Mitoxantrone + Etoposide + Cytarabine [MEC]: 1, ME: 1), hypomethylating agents in 5 (28%), and haploidentical natural killer (NK) cell adoptive transfer following lymphodepleting chemotherapy in four (22%) patients. At the time of HCT, 13 (72%) and 5 (28%) patients were in first and second morphologic leukemia-free aplastic state, respectively.

Transplant conditioning was reduced-intensity in 10 (56%) and myeloablative in 8 (high-dose total body irradiation [TBI]-based: 4) patients. The donor was matched unrelated (MUD) in 10 (56%), matched sibling in 5 (28%), and umbilical cord blood (UCB) in 3 (17%) patients. Three (17%) transplants were cytomegalovirus (CMV) seronegative donor to seronegative recipient. Graft-versus-host disease (GVHD) prophylaxis was calcineurin inhibitor-based in 15 (83%) patients, anti-thymocyte globulin (ATG) was used in 4 (22%) patients, and post-transplant cyclophosphamide was used in 1 (6%) patient. Two (11%) patients received sirolimus-based prophylaxis. The median (range) interval between the last treatment and HCT was 53 (23–88) days and the median (range) diagnosis-to-HCT interval was 3.8 (1.8–35.0) months.

There are six survivors (3+ months: 2 patients; 6+ months: 2 patients; 5+ years: 2 patients; all measured from allo-HCT). Primary graft failure did not occur in any patient. The cumulative incidence of grade II–IV acute GVHD by day 180 was 50 (25–75)% and chronic GVHD did not occur in any patient. The cumulative incidence of relapse at 6 months and 1 year was 18 (5–36)% and 25 (7–46)%, respectively. Relapse-free survival at 6 and 12 months was 47 (22–68)% and 40 (17–62)%, respectively. The corresponding estimates for OS were 65 (38–83)% and 38 (21–67)%. The cumulative incidence